In search of prognostic indicators for lymphomatoid papulosis: A retrospective study of 123 patients

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Background: Lymphomatoid papulosis (LyP) is a benign recurrent papulonodular skin eruption with histologically malignant features that sometimes (10%-20%) progresses to lymphoma.

Objective: We retrospectively evaluated the clinical course of patients with LyP and identify prognostic factors possibly indicating a malignant course.

Methods: Clinical, histopathologic, and immunologic features and molecular genetics were examined and correlated with clinical course and outcomes. Immunophenotyping and chemokine profiling were performed in select skin biopsy samples. A follow-up questionnaire was sent to patients. Clinical course and association with neoplastic disorders were correlated with LyP subtypes, molecular genetics, and immunophenotyping studies.

Results: Of 123 patients with LyP (1991-2008) followed up a mean of 4 years (range, 2 months to 14 years), 17 (14%) had an associated hematologic malignancy, 8 of which were mycosis fungoides. Histopathologic analyses demonstrated classic LyP type A (n = 69), B (n = 13), or C (n = 6), and a slight predominance of T-cell CD8 marker expression for type A. More than one type of lesion was present in 9 patients with a higher incidence of hematologic malignancies. T-cell receptor gene rearrangement positivity was about two times higher, with LyP associated with hematologic malignancy (82% vs 44%; odds ratio 5.7; $P = .02$). Chemokine studies in a subset of 25 patients showed chemokine receptor (CCR) $CCR4^+$ and thymus and activation-related chemokine ($TARC^+$) in all LyP types and $CCR3^+$ and chemokine-related receptor (CXCR) $CXCR3^+$ in types B and C.

Limitations: Retrospective study design is a limitation.

Conclusions: Positive T-cell receptor gene rearrangement or diagnosis of mixed-type LyP may be a prognostic indicator of disease more prone to progress to lymphoma. (J Am Acad Dermatol 2012;66:928-37.)

Key words: CD30 lymphoproliferative disorder; chemokines and chemokine receptors; cutaneous lymphomas; lymphomatoid papulosis; T-cell gene rearrangement.

As originally described by Macaulay[1] in 1968, lymphomatoid papulosis (LyP) is a recurrent papulonodular skin eruption with histologically malignant features but an often benign and indolent clinical course. Now, more than 40 years later, we are still unable to identify the 10% to 20% of patients in whom lymphoma will develop, whether it be $CD30^+$ anaplastic large-cell lymphoma (ALCL), mycosis fungoides (MF), or Hodgkin disease.[2-8] The current World Health Organization (WHO)—European Organization for Research and Treatment of Cancer (EORTC) classification has listed LyP as a primary, cutaneous, $CD30^+$ lymphoproliferative disorder.[9,10] Classifying the disorder from a pathologic perspective has yielded 3 histologic types of LyP: type A, type B, and type C. The most common of these is type A, which has large atypical lymphocytes resembling Reed-Sternberg

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cells of Hodgkin lymphoma with a mixture of inflammatory cells in a wedge-shaped distribution throughout the dermis. Type B has small, cerebriform, lymphocytic cells in a bandlike pattern, and type C is characterized by a monotonous population of large atypical cells and fewer inflammatory cells than the other two types. A previous report from our institution noted that lymphocytes in type B were found to be mostly $CD30^-$ (24/31 [77%]), in contrast with types A and C.[3] T-cell antigens typically expressed by any of the atypical lymphocytes are CD2, CD3, and CD4, with sparse or absent staining of CD1, CD7, and CD8,[11-19] although recent evidence suggests that many LyP lesions may actually be CD8 predominant.[16] Clonal T-cell receptor gene rearrangement (TCRGR) has been observed in 50% of LyP cases,[2,19-24] the significance of which remains unclear.

Chemokine and chemokine receptors (CCRs) have been of recent interest, particularly in defining cutaneous lymphomas.[25-32] The trafficking of lymphocytes to the skin, a key feature of immune surveillance, is accomplished by a coordinated sequence of events involving chemokine-induced migration of leukocytes into target tissues and the homing of lymphoma cells to the skin.[25,26] In MF, the pattern of expression has been correlated with tumor phase and progression.[26,29] The chemokine-related receptor (CXCR) CXCR3 has been shown to be expressed in early stages of MF but not in the tumor stage, whereas expression of the chemokine receptor CCR4 was noted in large-cell transformation of MF[26,29-31] and CCR3 has been shown to be expressed in primary cutaneous ALCL.[26] The few studies available on LyP that focus on chemokine expression have been inconclusive.[26,28]

The main objective of this study was to evaluate the clinical features of 123 patients with LyP seen at our institution during the period from 1991 to 2008, thus bringing continuity to our first report of 53 patients, which encompassed the previous 25 years.[2] Three substudies were also performed to analyze the histopathologic, immunophenotypic, molecular genetic, and chemokine characteristics of all available LyP specimens from this set of patients and the correlation between these findings and prognoses. Our findings on 14 pediatric patients (aged <20 years) have been reported separately.[16]

CAPSULE SUMMARY

- Lymphomatoid papulosis is a benign skin eruption designated as a lymphoproliferative disorder. No test can identify the 15% of patients in whom the condition progresses to malignant lymphoma.
- We studied 123 patients with lymphomatoid papulosis, 14% of whom had an associated hematologic malignancy.
- A positive T-cell receptor gene rearrangement and/or a diagnosis of mixed-type lymphomatoid papulosis may help identify those cases more likely to progress to lymphoma. The CD8 phenotype does not appear to be a poor prognostic sign.

METHODS

This is a retrospective analysis of all patients with both clinical and histopathologic diagnosis of LyP seen at Mayo Clinic, Rochester, MN, from 1991 to 2008. The inclusion criterion for the main group of patients was the clinical and histopathologic diagnosis of LyP. Patients who did not satisfy both criteria were excluded. In all, 123 patients were identified who met the inclusion criteria. Studies on the biopsy samples, designated as substudies, were performed as described below. Statistical analysis was used to assess the risk between the different study groups. The Fisher exact test and contingency tables were used to calculate the odds ratio (OR). Results were considered significant at P less than .05.

The Mayo Clinic Institutional Review Board approved the study, and all patients signed an authorization form for research.

Clinical features (N = 123 patients with LyP)

An electronic search of medical charts using the words "lymphomatoid," "papulosis," or both for the years from 1991 to 2008 retrieved 310 cases, which were carefully reviewed. Only those patients who matched the inclusion criteria of documented clinical and histopathologic diagnosis of LyP were included in the study, for a total of 123 cases.

Follow-up information was available either by chart review or letter questionnaire for 92 patients. Of the 31 remaining patients, some were seen as referrals and, although their biopsy specimens were read by our dermatopathologists, there was no specimen block available for further studies; others simply did not respond to the questionnaire.

Histopathologic and leukocyte immunophenotyping substudy (n = 133 LyP biopsy specimens from 97 patients)

After the 123 patients with LyP were identified as previously described, we performed a search to retrieve their archived biopsy specimens. We were